

REVIEW

Milroy disease and the VEGFR-3 mutation phenotype

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Primary congenital lymphoedema (Milroy disease) is a rare autosomal dominant condition for which a major causative gene defect has recently been determined. Mutations in the vascular endothelial growth factor receptor 3 (VEGFR-3) gene have now been described in 13 families world-wide. This is a review of the condition based on the clinical findings in 71 subjects from 10 families. All 71 individuals have a mutation in VEGFR-3. Ninety per cent of the 71 individuals carrying a VEGFR-3 mutation showed signs of oedema, which was confined in all cases to the lower limbs. In all but two cases onset of swelling was from birth. Other symptoms and signs included cellulitis (20%), large calibre leg veins (23%), papillomatosis (10%), and upslanting toenails (10%). In males, hydrocoele was the next most common finding after oedema (37%). Thorough clinical examination of these patients indicates that there are few clinical signs in addition to lower limb oedema. Rigorous phenotyping of patients produces a high yield of VEGFR-3 mutations.

Meige's family differed in that his cases had onset of oedema at puberty and a description of what appears to be acute cellulitis was given.

With the advent of molecular medicine the underlying cause of at least three types of dominantly inherited lymphoedema has been elucidated. Ferrell *et al*⁸ and Evans *et al*⁹ published evidence for a gene locus for congenital familial lymphoedema (Milroy disease) at chromosomal location 5q35. The gene mutated at this position was found to code for vascular endothelial growth factor receptor 3 (VEGFR-3), a member of the tyrosine kinase receptor family.^{8,9} This receptor, activated by VEGF-C and VEGF-D, is required for lymphatic development during embryogenesis.¹⁰ All mutations found to date have been located in either of the two intracellular kinase domains and are presumed to interfere with tyrosine kinase activation.^{8,9}

Mutations in the transcription factor gene, *FOXC2*, have been described in lymphoedema-distichiasis syndrome.^{11,12} In this condition the onset of oedema is usually at or after puberty. In addition to oedema, individuals with this condition often have distichiasis (aberrant eyelashes growing from the meibomian glands). The extra lashes are frequently the presenting complaint in this condition as their development precedes the oedema. A recent study has found an increased incidence of ptosis, varicose veins, cleft palate, and congenital heart disease amongst mutation carriers.¹³

More recently, mutations in the *SOX18* gene have been reported to cause hypotrichosis-telangiectasia-lymphoedema syndrome.¹⁴ The mutations in this gene are associated with a very distinct phenotype—hypotrichosis and lymphoedema presenting in childhood and telangiectasia or vascular naevi, particularly on the palms and soles. To date there have been no studies looking for mutations in *SOX18* in patients with isolated primary lymphoedema.

However, most families with lymphoedema do not have changes within the genes discovered thus far, indicating that there are several more genes for lymphoedema to be discovered. Further evidence for genetic heterogeneity comes from studies of lymphoedema families in which the results are not consistent with linkage to either the *VEGFR-3* or *FOXC2* loci.¹⁵

Thirteen mutations have now been located in *VEGFR-3* in families with primary congenital lymphoedema^{8,9,16} although to date the detailed clinical phenotype of some of these families has been lacking. In this paper we describe the

In 1892 William Milroy described a family with congenital onset lymphoedema which was heritable, painless, non-progressive, and confined to the lower limbs.¹ In his paper Milroy described a family consisting of 97 members, of whom 26, in six generations, had oedema. Some 35 years later Milroy attempted to follow up this family and was successful in locating 36 additional descendants.²

In William Osler's, *The principles and practice of medicine*, lymphoedema was first designated with Milroy's name.³ The lack of understanding of the cause of the condition is highlighted by the placing of the condition in the subsection of "Angioneurotic oedema" in the chapter entitled "Diseases of the nervous system". In his follow up paper of 1928, however, Milroy suggested that lymphatic blockage may be the underlying cause, but did not dismiss the idea of a vasomotor abnormality.⁴

Primary lymphoedema is chronic tissue swelling, most commonly present in a lower limb, resulting from an intrinsic abnormality of lymph drainage.⁴ The term Milroy disease has unfortunately been increasingly used as a blanket term for all types of primary lymphoedema, whether or not the phenotype conforms to the original description by Milroy. Indeed Milroy himself did not clearly recognise that the type of lymphoedema he described was of a different aetiology to that described in 1898 by Henry Meige.⁵

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Abbreviations: VEGFR-3, vascular endothelial growth factor receptor 3

clinical phenotype of 71 patients from 10 families. All patients have mutations in one of the kinase domains of the *VEGFR-3* gene.¹⁶

METHODS

Patient ascertainment

Twelve families were originally ascertained on the basis of a family history of congenital lymphoedema. Seven probands were ascertained following referral to local lymphoedema clinics. Of the remaining five, two were referred by interested physicians and three, including two from the USA, self referred. All other family members subsequently enrolled in the study were contacted via the proband in the first instance. Two of the 12 families were excluded from this study as no *VEGFR-3* mutation was identified although their clinical features were consistent with a diagnosis of Milroy disease.

Clinical phenotyping

In total, 211 individuals from the 10 families were clinically examined by at least one of the authors (GB, AHC, PSM, SM). Features of particular relevance included lymphoedema, venous abnormalities, and facial dysmorphism. Characteristic skin and nail changes, such as hyperkeratosis, skin thickening, increased skin markings, and fungal infections were also sought. Patients were questioned regarding their past medical history, family medical history, occurrence of cellulitis, venous problems, treatments, age at onset of swelling, and progression of the oedema over time. Care was taken to specifically exclude syndromes with a known genetic cause such as lymphoedema-distichiasis syndrome, hypotrichosis-lymphoedema-telangiectasia syndrome, and Turner and Noonan syndromes.

Molecular diagnosis

Initially, 12 affected probands with family histories of congenital lymphoedema were screened, looking for mutations in the *VEGFR-3* gene. The results in all 12 families were consistent with linkage to chromosome 5q35. In 10 families, the entire gene was sequenced and eight mutations found. In the remaining two families, in which mutations were found, only the kinase domains were studied. Following discovery of a putative mutation in the proband, samples from all available affected and unaffected family members were analysed to ensure segregation of the sequence change with the affected phenotype.

Lymphography/lymphoscintigraphy

Ten patients (from five families) had previously undergone isotope lymphography (lymphoscintigraphy) or traditional x ray lymphangiography. Results of gamma camera isotopic scans were based on the images obtained and comparing the uptake of radioactivity in regional lymph glands relative to the injected dose in the foot.¹⁷

RESULTS

The clinical findings are presented in table 1.

Family demographics

Following ascertainment via an affected proband, 211 individuals from 10 families, including unaffected spouses, were examined because of a family history of congenital lymphoedema. Of these, 64 (31M/33F) were found to be clinically affected with limb swelling or characteristic skin changes. All those thought to be clinically affected were found to carry *VEGFR-3* mutations. Seven (10%) clinically unaffected individuals (4M/3F), including three obligate gene carriers, were found to carry mutations in the absence of clinical signs. Following clinical review of these gene carriers, in light of their molecular analysis, initial impressions of their

Table 1 Clinical findings

| | Number | M/F |
|--|-------------|-------|
| Total patients with <i>VEGFR-3</i> mutations | 71 | 35/36 |
| Lymphoedema present | 64/71 (90%) | 31/33 |
| Age of onset of oedema | | |
| Congenital | 62/64 (97%) | 31/31 |
| Non-congenital | 2/64 (3%) | 1/1 |
| Extent of oedema | | |
| Below knee | 60/64 (94%) | 28/32 |
| Above knee | 4/64 (6%) | 3/1 |
| Bilateral oedema | 55/64 (85%) | 26/29 |
| Symmetry of oedema | | |
| Symmetrical swelling | 35/64 (55%) | 14/21 |
| Right>left | 15/64 (23%) | 11/4 |
| Left>right | 5/64 (8%) | 1/4 |
| Unilateral swelling | | |
| Right | 4/64 (6%) | 2/2 |
| Left | 5/64 (8%) | 3/2 |
| Hydrocoele | 13/35 (37%) | |
| Prominent veins | 16/71 (23%) | 9/7 |
| Cellulitis | 14/71 (20%) | 11/3 |
| "Ski jump" toenails | 10/71 (14%) | 5/5 |
| Papillomatosis | 7/71 (10%) | 5/2 |
| Urethral abnormality | 3/71 (4%) | 3/0 |

F, female; M, male.

unaffected status have not changed. As only two out of 64 affected gene mutation carriers developed oedema later in life, it is unlikely, though still possible, that these seven individuals will develop oedema.

Clinically there was marked inter- and intrafamilial variation in the degree of oedema, ranging from only toes affected to bilateral swelling to the groin.

Age of onset

Of the 64 clinically affected individuals, 62 reported swelling from birth, with the two remaining individuals (1M/1F) reporting swelling first noted at ages 25 and 46, respectively. In two cases, where severe swelling of the dorsum of the foot was present at birth, oedema had reduced substantially by the age of 5. In all other cases the extent of swelling reportedly remained largely unchanged over time in contrast to lymphoedema-distichiasis, which tends to progress. Sclerosis of the skin with limited pitting seems to be a characteristic of Milroy disease and presumably limits swelling.

Distribution of swelling

Bilateral leg swelling was present in 55/64 (26M/29F) individuals. Of these, leg swelling was asymmetrical in 20 (12M/8F). An additional nine individuals were affected unilaterally (5M/4F). Expression ranged from no clinically evident swelling in seven individuals (10%) to severe, bilateral swelling to the groin in two cases. Gender did not influence the degree of swelling.

Urological abnormalities

Of the 35 males with *VEGFR-3* mutations, 13 (37%) had developed a hydrocoele. In three of the 13 cases, bilateral hydrocoeles were reported, including a gene carrier with no lymphoedema when examined at the age of 42. Three male patients underwent surgery in childhood for urethral abnormalities; two were described as urethral stricture and the third as mild hypospadias. A fourth individual had an operation on the penis at birth but details were unclear and this may have been for severe oedema causing phimosis.

Veins

True varicose veins were present in only three individuals, with only two females having undergone surgical procedures for the condition. Sixteen individuals were however noted to



Figure 1 Tense prominent dilated veins noted in 16 patients (reproduced with permission).

have large calibre but non-tortuous long saphenous veins (fig 1). These veins were not painful and not associated with any skin signs of venous disease.

Other phenotypic abnormalities

Upslanting of the nail on the big toe ("ski-jump" toenails), apparently present from birth, was noted in 10 patients (fig 2). In eight individuals the nails on the big toe were abnormally thickened and yellow in colour. Papillomatosis was noted on the toes of seven individuals. In all cases the papillomas were present over the base of the second toe (fig 3). All of these features can be secondary to lymphoedema of any cause.

There were no consistent dysmorphic features in the affected individuals.

Infection

Cellulitis was reported as a recurring problem in 14 cases (11M/3F) with males significantly more likely to be affected (Fisher's exact test, $p = 0.015$). Several patients were taking long term prophylactic antibiotics. Generalised problems with immunity were not evident from medical histories.

Lymphangiography/lymphoscintigraphy

Ten patients had undergone either lymphangiography or lymphoscintigraphy. In all four cases where lymphangiography was successful, lymphatic hypoplasia was noted. Two attempts at lymphangiography failed due to lack of

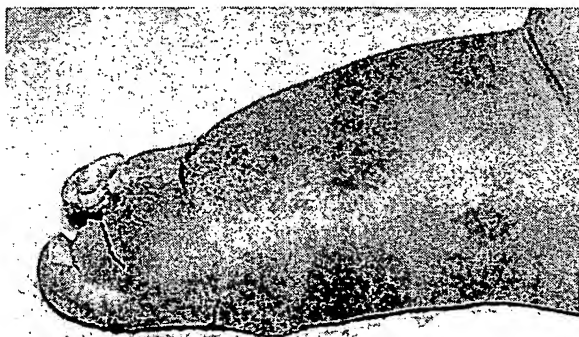


Figure 2 Upslanting ("ski-jump") toenails (reproduced with permission).



Figure 3 Papillomas over base of second toe (reproduced with permission).

lymphatics in the foot. The lymphoscintigram results in all six cases showed no, or little, uptake by peripheral lymphatics in the foot and consequently no, or little, uptake in the ilio-inguinal nodes (fig 4).

Treatment

On presentation to the clinic only 16 patients were having active treatment for lymphoedema. Treatments were limited to massage and compression with hosiery or pneumatic therapy. Two female patients had undergone surgery; one had unilateral reduction surgery in childhood, while the other had removal of papillomas from the dorsum of the toes in her twenties.

Molecular results

All 71 patients had mutations within one of the two kinase domains of *VEGFR-3*. Details of all mutations have previously been published.¹⁶

DISCUSSION

Phenotypic abnormalities are described in 71 individuals with mutations in *VEGFR-3* (Milroy disease). Seven were found to

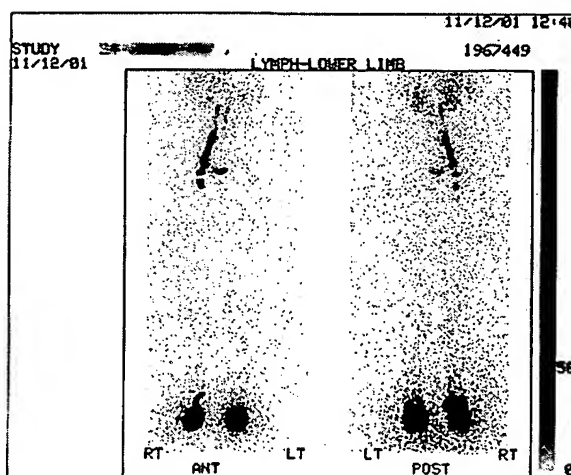


Figure 4 Lymphoscintigraphy: depot injections in right and left foot. There is tracer uptake in the right ilio-inguinal nodes but no uptake on the left due to failure of peripheral lymphatic uptake. This patient had unilateral left leg swelling.

carry disease causing mutations but were clinically unaffected. Of the 64 clinically affected individuals with *VEGFR-3* mutations, below knee swelling, usually bilateral, was the most consistent finding. While onset at birth has been a requirement for the clinical diagnosis of Milroy disease, two individuals with mutations appeared to develop swelling much later in life, although it is possible subtle early changes may have been missed. Other investigators have also found that the majority of *VEGFR-3* mutation carriers develop congenital swelling but rare cases appear later in life.¹⁴ In males, hydrocoele is the next commonest manifestation after swelling. Cellulitis is significantly more common in males, as was reported in association with lymphoedema-distichiasis syndrome.¹¹

Milroy disease has frequently been confused with other forms of congenital lymphoedema. This study excluded families without mutations in order to refine the phenotype of those with clinical Milroy disease and a *VEGFR-3* mutation. Clearly, not all individuals with Milroy disease will have identifiable mutations in *VEGFR-3*. Milroy disease should be considered if the lymphoedema is congenital and confined to the lower limbs. The swelling is frequently "woody" in nature and associated with secondary changes which include deep creases over the toes, small dysplastic ("ski jump") toenails, and papillomas. The prominent wide calibre leg and foot veins are often a good clue to the underlying diagnosis as they are not seen with other causes of congenital lymphoedema.

Unlike other syndromes associated with lymphoedema, there are few associated abnormalities. Apart from hydrocoeles and some urethral abnormalities, there were no major structural abnormalities or consistent dysmorphic features.

VEGFR-3 is one of the most important genes responsible for lymphangiogenesis. Transgenic mice that are homozygous for *VEGFR-3* mutations die before birth as a consequence of severe cardiovascular abnormalities.¹⁹ Chy mice (*VEGFR-3*^{-/-}) and mice in which the *VEGFR-3* receptor is blocked, develop hind limb oedema similar to Milroy disease.²⁰ In these mice fluorescence microlymphangiography failed to demonstrate functioning skin lymphatics (as was described in three human cases of Milroy disease²¹). Chy mice develop chylous ascites and some die soon after birth. In those that survive, chylous ascites resolves spontaneously never to reappear. No cases of chylous ascites have been described in those patients with *VEGFR-3* mutations. To what extent transient ascites occurs in utero but then resolves is uncertain, but there have been no reports of this occurring.

Despite the germline mutation, lymphoedema appears to develop only in the lower limbs of humans or the hindlimbs of transgenic mice, but the reason for this is not clear. The onset of oedema at birth, before walking begins, suggests that orthostatic factors are not responsible for the limitation of oedema to the lower limbs. A failure to detect peripheral lymphatics with vital dyes prior to radiocontrast lymphography²² or a failure of uptake of radiotracers by initial lymphatics during lymphoscintigraphy, as seen in six of our patients, would be in keeping with a failure in development of the most peripheral lymphatic vessels in the lower limbs.

Although there was a suggestion of hand swelling in one patient examined at the age of 1 year, our experience has shown that it is often difficult to differentiate between oedematous and normal skin in young children.⁷ Follow up of this patient has not been possible.

Because *VEGFR-3* is involved in cardiovascular development before the receptor becomes restricted to the lymphatic endothelium, one could have expected some cardiovascular abnormalities, but none were observed. The finding of large calibre long saphenous veins needs further investigation.

Venous disease does not obviously develop in Milroy disease, unlike in lymphoedema-distichiasis syndrome.¹¹

The finding of urethral stricture in two patients and hypospadias in a third is of interest. The majority of cases of urethral stricture in the general population are acquired, with the congenital form being extremely rare. Hypospadias occurs in less than 1% of male births. Our findings may be coincidental, but with an incidence of 8% in males in our series it is likely to be a true association, although there is no clear common embryological origin between the urethra and lymph system.²³

The apparent non-penetrance of oedema in 10% of individuals with a *VEGFR-3* mutation is important from a counselling point of view, both in terms of reproductive risk estimation and possible cosmetic effects of the condition.

For clinical purposes we propose that the term Milroy disease should be reserved only for those cases of primary lymphoedema which conform to the criteria proposed by Milroy: familial (autosomal dominant inheritance), congenital onset, non-progressive, lower limb involvement. However, theoretically, new dominant mutations may occur, or the parent may be non-penetrant. *VEGFR-3* analysis in these situations would be helpful.

Theoretically, gene therapy would be an option for treatment particularly as successful reversal of the phenotype has been achieved in transgenic mice.^{24 25}

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This study had the approval of the Wandsworth Local Research Ethics Committee and the University of Connecticut Health Center Institutional Review Board. Written consent was obtained from all participants or, in the case of a child, from their parent.

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